GD57 (S) A29

PETROL VAPOR
==========

Effect on Pulmonary Surfactant:

increase of sulphated mucins in rat bronchial epithelium (Jones et al., Brit. J. Exp. Pathol. 54: 229, 1973)

dose-dependent decrease of amount of surfactant to less than 5o o/o after 45 d inhalation (Le Mesurier, S. et al., Proc. Aust. Biochem. Soc. 12: 58, 1979)+

Inhalation:

not accompanied by change of RNA and DNA synthesis, but amount of surfactant in lavages reduced (Le Mesurier, S.M. et al., Pathology 11: 81-87, 1979)+

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arbeitet werden können. Durch den reichen, sehr komprimiert dargebotenen Informationsgehalt gewinnt der Band ferner den Charakter eines Nachschlagewerkes, ohne dabei seine Funktion als einführendes Lehrbuch zu verlieren. Das Taschenbuch eignet sich vor allem für Studenten der Biochemie und ihrer Nachbardisziplinen, wie Mikrobiologie, Botanik, Zoologie, Medizin, Pharmazie, Landwirtschaft, Lebensmittelchemie, Chemie und Physik. Es erleichtert dem Dozenten an Hochschulen die Grundlagen der Biochemie in den Vorlesungen rascher zu erörtern und damit mehr Zeit für die Berücksichtigung spezieller Bereiche und jüngster Forschungsergebnisse der Biochemie zu gewinnen. Das Werk bietet außerdem Chemikern sowie Biologen in der Industrie, an Gymnasien und Fachschulen eine leicht zu erschließende Einarbeitungs- und Orientierungshilfe.

Siegfried Pfeifer

Biotransformation von Arzneimitteln
Band 1 und 2

Verlag Chemie, Weinheim 1977, 484 und 424 Seiten, DM 90,– und DM 70,–

Das Werk „Biotransformation von Arzneimitteln", Band 1–3, bringt eine neuartige, durch Verwendung von zahlreichen Abkürzungen und Symbolen stark verdichtete Darstellung der Ergebnisse, die auf diesem wichtigen Gebiet der Arzneimittelforschung erzielt wurden. Die nach einheitlichen Gesichtspunkten bearbeiteten Monographien geben dem Leser die Möglichkeit, sich schnell über alle wichtigen Fragen des Fachgebietes zu orientieren.

Angeführt werden die isolierten bzw. nachgewiesenen Metaboliten bei den einzelnen Tierspezies und beim Menschen, die Ausscheidungsverhältnisse, Bemerkungen über die Abhängigkeit der Biotransformation bzw. der Exkretion von Alter, Geschlecht, Krankheiten und der Applikationsart. Weiter behandelt das Werk die Pharmakologie und Toxikologie der Metaboliten, die Wechselwirkungen zwischen Arzneimitteln und sonstigen Substanzen, insbesondere durch Enzyminduktion und Hemmung des Metabolismus. Es werden weiterhin Hinweise auf die in den zitierten Originalarbeiten benutzten analytischen Verfahren gegeben, die zur Isolierung und Strukturaufklärung von Metaboliten sowie zur Distribution und Pharmakokinetik eingesetzt werden.

Band 1 enthält Verbindungen, die den folgenden Gruppen zuzuordnen sind: antibakterielle Sulfanilamide, Antidiabetika, Antiepileptika, Psychopharmaka, Sedativa-Hypnotika, synthetische Steroidhormone (Anabolika, Androgene, Gestagene, Kortikoide, Östrogene) und Östrogene anderer Struktur.

Der Konzeption und Ausführung des Bandes 1 entsprechend enthält Band 2 211 Monographien über Substanzen der folgenden Wirkstoffklassen: Analgetika, Antineuralgika, Antirheumatika, Antiinflammatoria (nichtsteroide Antiphlogistika), Analgetikaantagonisten, Antiarrhythmika, β-Rezeptorenblocker, Antihypertensiva, Chemotherapeutika (Nitroheterozyklen), Koronardilatatoren, Tuberkulostatika.

Band 3 erscheint 1978.

Dennis Piszkiewicz

Kinetics of Chemical and Enzyme Catalyzed Reactions

Oxford University Press, Oxford 1977, 248 pages, 55 figures, £ 5,75

This volume is intended to serve several functions. It is meant as a means of teaching kinetics to advanced undergraduate and graduate students. A background knowledge

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in organic chemistry and some knowledge of calculus is assumed, and while a familiarity with biochemistry and chemistry would be useful, it is not essential. It is also intended as a primer for reading papers in the literature dealing with kinetics. In addition, it will serve as an introductory, practical handbook, and will be a compact reference of common methods for graphical analysis.

M. Roche e Silva (Hrsg.)

Histamine and Anti-Histaminics

Handbuch der experimentellen Pharmakologie, Band 18

Teil 1: Histamine. Its Chemistry, Metabolism and Physiological and Pharmacological Actions

Teil 2: Histamine II and Anti-Histaminics

Springer-Verlag, Berlin Heidelberg 1977, 991 und 600 Seiten, DM 230,– und DM 272,–

This part completes volume XVIII of the Handbook, which constitutes the most comprehensive survey of the whole histamine problem covering practically all fields of experimental pharmacology and medicine, in which histamine participates as chemical mediator. As a source of information of the histamine problem, these two volumes will for many years stand as unique collection of data and bibliographical references to aid people working in the field, as well as clinicians pathologists and pharmacologists interested in the related field of chemical mediation of the inflammatory reaction and clinicalmen, using antihistaminics as therapeutics agents.

John R. Sabine

Cholesterol

Marcel Dekker Verlag, Basel 1977, 512 Seiten, sfr. 82,–

Cholesterol provides thorough coverage of present knowledge of mammalian cholesterol metabolism. The book is organized around three basic issues: the role of cholesterol in mammalian systems and the mechanisms by which it enters and leaves these systems; the physiological and pharmacological controls that regulate this ingress and egress; the evidence implicating cholesterol in the etiology of various diseases, particulary atherosclerosis, cancer, and cholelithiasis.

Despite today's enormous popular scientific interest in cholesterol, there has been no comprehensive review of certain important aspects of the field – cholesterol in the blood, the pharmacological control of cholesterol synthesis, cholesterol and cancer, to mention just a few – for at least twenty years.

Cholesterol answers this need in a highly readable style that is accessible to those with minimal scientific training as well as to specialists seeking an up-to-date overview of the field. This valuable synopsis is necessary reading for physiologists, biochemists, biologists; for practitioners in related fields, such as physicians or veterinarians; and for students on the graduate and undergraduate level.

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GD55 (S) A24

PHASE 2 REACTIONS
==========

inhibition of phase 2 reactions, 2oo micromol/l, rat hepatocytes (Orrenius, S., Naunyn-Schmiedeberg's Arch. Pharmacol. 313 S: R4/16, 198o)+

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GD56 (S) B3o

PHENOL-O-METHYLTRANSFERASE
==========

Occurence:

microsomes of mammalian liver and lung (Holbrook, D.J.jr. in Hodgson, E., Guthrie, F.E. (Eds.): Introduction to Biochemical Toxicology, Amsterdam, Elsevier, 198o, p. 32o)+

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GD82 (S) B15 LA (PW) 26.Aug.81

PHENYLALANINE
==========

Determination:

AA converted with phenylalanine ammonia lyase to p-coumarate (trans-cinnamate) + ammonia (Shen, R., Abell, C.W., Science 197: 655 (1977) and P.L. Analects 9, 1981+)

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PHORBOL ESTERS
==========

Assay:

murine erythroleukemia adhesion assay according to Yamasaki (Weinstein, I., Evaluating substances for promotion, cofactor effects and synergy in the carcinogenic process. J. Environ. Path. and Toxicol. 3: 89-1o1, 198o+)

Receptors:

high-affinity receptor for phorbol esters detected with 3H-phorbol-dibutyrate in membranes of all mammalian tissues. Highest levels of specific binding found in brain. Although .LT.1 0/0 of the binding could be found in the cytosol, the addition of phospholipid to brain cytosol can reconstitute the aporeceptor. Therefore the receptor requires phospholipid for function. (mu)
(Leach, K.L., James, M.L. and Blumberg, P.M., Characterization of a specific phorbol ester aporeceptor in mouse brain cytosol, Proc. Natl. Acad. Sci. 80: 4208-4212 (1983))

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PHORBOL ESTERS

Chemistry:

esters of polyfunctional diterpene alcotrols

Biological Activities:

(1) cocarcinogenic and/or
(2) antileukemic and/or
(3) inflammatory (present in all cases)
(Schmidt, R.J. and Evans, F.J., Arch. Toxicol. 44: 279-289, 1980)+

Stimulation of proliferation,
Hyperplasiogeny,
Inflammatory action,
Promotor activity
ODC-stimulation
) see PROMOTORS

4-O-methyl ether of TPA
Ti8: 12-O-tetradeca-2-cis, 4-trans-6,8-tetra-enoylphorbol-13-acetate
(Euphorbia tirucalli) see PROMOTORS

Action on Peritoneal Macrophages:

Reduction of lag phase for macr.-mediated cytolysis of target cells (Keller, Exp. Cell. Res. 121: 124, 1979)+

Phorboldibutyrate (PDB):

weak promoting agent

Promoting Activity in vivo:

phorbol: o
PDB: 2
TPA: 4

Promoter Activity:

Esterification at R1 and R2 required (Weinstein, I., Evaluating substances for promotion, cofactor effects and synergy in the carcinogenic process. J. Environ. Path. and Toxicol. 3: 89-101, 1980+)

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GD27 (S) B18 (PW)

PHOSPHATE
=========

Determination:

(1) Fiske-Subarow-Method:
formation of 12-molybdophosphoric acid in acid medium, subsequent reduction to heteropoly molybdenum blue.

(2) fluorometric method:
determination as Rhodamine B molybdophosphate (Kirkbright et al. Anal. Chem. 43: 1434, 1971)

(3) spectrophotometric method:
formation of insoluble blue violet dye salt, crystal violet-12-molybdophosphate, kept in colloidal solution by action of surface active agent. Excess of free dye protonated to form a green onion. Unchanged dye salt determined at 560 nm. Time requirement: approx. 30 min. Application: human control sera
(Fogg et al., Anal. Chim. Acta, 88: 197-200, 1977#)

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4.Jun.84 GD15 (LIT) B1 (RZ)

PILOCARPINE (sympathomimetic)
==========

stimulation of release of surfactant from type 2 pneumocytes (Pysher, T.J., Konrad, K.D. and Reed, G.B., Effects of hydrocortisone and pilocarpine on fetal rat lung explants, Lab. Invest. 37: 588 (1977))

increased ciliary beat frequency (rt)

increased size and number of mucus producing cells (rt)

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PITUITARY GLAND (HYPOPHYSIS)

Glandotropic Hormones:

Adenohypophysis:

TSH : → stimulates thyroxine
FSH : → stimulates testosterone
ICSH: -
ACTH: → stimulates corticosterone
STH : → stimulates growth
MSH : → stimulates melanin formation

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DRWK/OA (OA2B23) (WS) 5.Oct.81

PNEUMOCYTES, TYPE 1
==========

most vulnerable lung cells (Witischi, Toxicol. 5: 267, 1976)

glucose-6-phosphate dehydrogenase, (cf.) may be used as a marker (Vijeyaratnam, Corrin, J. Pathol. 1o8: 1o5, 1972)

Morphology:

small, flat to cuboidal, nucleus occupies greater part of the cell, surrounded by thin rim of cytoplasm. Few Mitochondria (Soranzo et al., J. Reticul. Soc. 23: 343, 1978, Li 2222)

Occurence:

line the alveoli and the pulmonary capillaries as endothelial cells

Toxicity:

(1) inhaled materials:

oxygen
ozone
nitrogen dioxide

(2) instilled materials:

FeCl3

CdCl3

(3) perfused materials (via blood stream):

paraquat
bleoycin
butylated hydroxytoluene
nickel carbonyl
bromocarbamide
pyrrolizidine alkaloids
iprindole (anti-depressant)
adrenaline
alpha-naphthylthiourea

(Witschi, H. et al., (Ed. Autor, A.P.): Biochemical Mechanisms of Paraquat Toxicity, Iowa: Academic Press, 1977, pp. 1-2o)

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POLYCHLORINATED BIPHENYLS (PCBs)

Synthesis:

catalytic chrorination of biphenyl

Analysis:

capillary GC

Induction of Cyt. P-45o:

incr. induction of P-45o, O-DEM and Aniline hydroxylase with increasing chlorine content. NADPH Cyt. C reductase and cytochrome b_5 barely influenced. Also induction of EH, glucuronosyl transferase 1 and 2 and GSH-transferase (Benthe, H.F. and Schmoldt, A., Naunyn-Schmiedeberg's Arch. Pharmacol. 313 S: R4/14, 198o)+

Carcinogenicity:

may stem in part from contaminating benzopyranes (Allen and Norbank in Hiatt et al., Origins of human cancer proliferation, Vol. 4, Cold Spring Harbor Lab., 1977)

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GD56 (S) B4 WS

POLYCHLOROBIPHENYLS
==========

AHM:

powerful, aspecific inducers of MFO

inductive capacities increased with the extent of chlorination

induction with hexa- and octachlorobiphenyls as well as di- and tetrachlorobiphenyls, when chlorine atoms occupy 3- and 4-positions (rt)
(De Bruin, A.: Biochemical Toxicology of Environmental Agents, University of Amsterdam: Coronel Laboratory of Occupational Hygiene: pp. 316)

Accumulation:

extensive in adipose tissue
(De Bruin, A.: Biochemical Toxicology of Environmental Agents, University of Amsterdam: Coronel Laboratory of Occupational Hygiene: pp. 316)

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GD27 (S) B21 (PW)

POLYCYCLIC HYDROCARBONS
==========

HPLC-Determination:

34 min. linear gradient from 6o/4o methanol/water to 1oo o/o methanol, RT, detection with combined variable and fixed wavelength UV-detectors.

254 nm: well suited for B(a)P but perylene interferes
29o nm: even better for B(a)P without perylene interference and for coronene, but other PHAs markedly reduced.
(Krstulovic et al., Anal. Chem. 48: 1383-1386, 1976+)

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GD57 (S) B21

POTASSIUM
=========

Determination by Flame Photometry:

serum/plasma: protein interference possible, dependent upon atomizer, sodium value slightly reduced, check with and without precipitation (Bergström, J., Scand. J. clin. lab. Invest. 68: 14-17, 38-41, 43, 74-75, 1962)+

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GD58 (S) A19

PORPHYRIA
=========

Kongenital Erythropoetic Uroporphyrie:

lack of uroporyrinogen-cosynthetase = uroporphyrinogen 1 = urine excretion. lethal disease, since uro. 1 is stored in all organs incl. skin = ligth-sensibilization = photodermatose (Buddecke, E. (Ed.): Grundriss der Biochemie, Berlin, Walter de Gruyter, 1971, p. 231)

Hepatic Porphyria:

delta-amino lävulinic acid synthetase repressed = excretion of delta-ALA = red colour or urine (Buddecke, E. (Ed.): Grundriss der Biochemie, Berlin, Walter de Gruyter, 1971, p. 231)

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Europäische Gesellschaft für Toxikologie

Tagung vom 25.—28. Juni 1978 in Berlin

Von Dr. H. Czerwek

Die Tagung hatte 3 Hauptthemen:

— Der Einfluß des neuroendokrinen Systems auf die toxischen Reaktionen nach Gabe von Hormonen und anderen Arzneimitteln.
— Entstehung einer adaptiven und malignen Lebervergrößerung durch Arzneimittel und Umweltverschmutzung.
— Organspezifität als ein toxisches Phänomen.

Die Vorträge zum ersten Themenkreis machten deutlich, daß im Zentrum des Geschehens das Hypothalamus-Hypophysen-System steht. Die Gabe von Sexualsteroiden verursacht in diesem System eine Veränderung, die mit einer Änderung der Hormonproduktion einhergeht und Anlaß zu spezifischen Hyperplasien und Tumorbildung ist. Durch diese Veränderungen sind auch Störungen bis zur Tumorbildung in den für die einzelnen Hormone entsprechenden Erfolgsorganen vorhanden. So ist z. B. der neuroendokrine Regulationsmechanismus bei Ratten und Mäusen für das Entstehen von Hypophysen- und Mammatumoren nach chronischen Östrogengaben verantwortlich. Diese Tumoren entstehen vorzugsweise bei vermehrter Prolaktinsekretion. Die Entstehung eines Mammacarzinoms durch Östrogengaben ist jedoch sehr stark speziesabhängig, und es scheint so zu sein, daß eher eine Entwicklung einer vorhandenen Carzinomanlage gefördert wird, als daß eine primäre carzinogene Wirkung vorhanden ist. Aus der starken Speziesabhängigkeit ist zu erklären, daß statistisch die Carzinomentstehung nach Hormongaben (Pille) bei Frauen nicht bewiesen werden kann.

In das Hypothalamus-Hypophysen-System können auch neuropsychotrope Substanzen eingreifen und beispielsweise über die Monoaminooxidase in den Regulationsmechanismus der Hormonproduktion der Hypophyse eingreifen.

Der zweite Themenkreis über die Entstehung von Leberveränderungen brachte in zahlreichen Referaten zum Ausdruck, daß eine große Menge chemischer Stoffe im Tierversuch bei wiederholter Zufuhr zu einer Aktivierung der am Metabolismus beteiligten Enzyme und zu einer Vergrößerung der Leber führen.

Damit ist eine Zunahme der Syntheseaktivität und der Zellteilung verbunden. Dieser Zustand könnte möglicherweise die Carcinomentstehung begünstigen.

Bei der durch die chemischen Substanzen hervorgerufenen Lebervergrößerung nimmt die Anzahl der Zellen mit mehreren Kernen zu, in gleicher Weise steigt auch der DNS-Gehalt und die DNS-Syntheserate.

Möglichkeiten zur Diagnose dieses Studiums sollen folgende sein:

In der Leber treten Zellen auf, die stark Glykogen speichern und teilweise in Herden angeordnet sind. Enzymhistochemisch kann es in frühen Stadien zu einer Vermehrung der Aktivität der Glykogen-Phosphorylase kommen. Im weiteren Verlauf nimmt die Aktivität der Phosphorylase und der Glucose-6-Phosphatase ab, während die Glycose-6-Phosphat-Dehydrogenase zunimmt. Im fortgeschrittenem Stadium verschwindet die Glykogenspeicherung als Zeichen einer weiteren Verschiebung des Zellstoffwechsels in Richtung der Entstehung eines Leberzellcarzinoms.

Eine ähnliche Entwicklung ist auch bei der Entstehung von Gallengangscarzinomen zu beobachten. Hier treten anstelle des Glykogen sauere und neutrale Mucopolysaccharide auf.

Die Entstehung eines Carzinoms resultiert aus der Einwirkung der Substanz oder eines ihrer Metaboliten auf die DNS im Bereich des für die Regulation der Zellvermehrung zuständigen Genoms. Besonders begünstigt wird die Carzinogenese, wenn es sich um Substanzen handelt, die das Zellwachstum anregen. Die Gefahr der Entstehung eines Lebercarzinoms ist am größten beim Zusammenwirken einer carzinogen Substanz mit einem enzymaktivierenden und eine Lebervergrößerung auslösenden Agens.

Im 3. Themenkomplex, der sich mit der Organspezifität toxischer Reaktionen befaßte, kam zum Ausdruck, daß eine differenzierte Organotropie verschiedener Substanzen durch den unterschiedlichen Enzymgehalt der Organe und der Bindungsfähigkeit der Substanz an die Makromoleküle der Zellen bedingt ist. In einer Reihe von Beispielen an speziellen Substanzen, u. a. auch Östrogenen, wurden die Aussagen erhärtet.

Ein Einzelreferat befaßte sich mit den Folgen der TCDD-Verseuchung im Gebiet von Seveso.

Eine große Zahl freier Vorträge, sowie eine neuerdings auf Kongressen fast obligatorische Posterschau, rundeten das Gesamtbild ab.

In der Geschäftssitzung wurden 81 neue Mitglieder aufgenommen. Für die nächste Tagung 1979 wurde nach Dresden eingeladen. Sie wird dort vom 11.—13. 6. stattfinden. Hauptthema ist die Besprechung der Methoden für die Testung einer Substanz auf immunologische, mutagene, carzinogene, embroytoxische und nephrotoxische Wirkung.

Anschrift des Verfassers: Dr. Harald Czerwek, Boehringer Mannheim GmbH, Sandhofer Str. 116, 6800 Mannheim

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PROLACTIN FDA-PROPOSED *PRECAUTION* FOR ANTIPSYCHOTIC DRUGS SUPPORTED by the agency's Psychopharmacologic Drugs Advisory Cmte., in an Nov. 13 vote. The proposed physician label "precaution" had resulted from an earlier cmte. recommendation for epidemiological studies to follow-up animal studies linking use of the drugs to breast cancer, FDAer Thomas Hayes, MD, noted. Pending completion of such studies, which Hayes said is unlikely any time soon, BuDrugs has "decided that as an interim measure, it is important to have wording on the label that would warn of potential problem for human beings from exposure to these drugs." Cmte. member Harold Stevens, MD/PhD, expressed a minority opinion: "In the absence of evidence – I think we ought to say nothing." He referred to the normal anxiety and suspicions of many patients taking antipsychotic drugs and said the prolactin precaution "increases the ambiguity, creating uncertainty with the patient. I don't think that's fair or practical."

¶ Hayes reported that FDA is currently waiting for the results of a comprehensive prolactin study being done by NCI. "If it fails to be conclusive the bureau might well undertake, of its own funding, a study designed to answer the question of effects on humans," FDAer Hayes said, adding: "It's just something we can't do very frequently." Results from the NCI study are not expected for another 12-18 months. "I don't understand the difficulty in designing such experiments," cmte. member Stevens asserted. "The population is readily available in the mental hospitals," suggesting studies be done to see if there was increased breast cancer within that group. "Many of these hospitals have 100% autopsy records."

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GERIATRIC DRAFT RESEARCH GUIDELINES RETURN TO BuDRUGS STAFFERS for reconsideration, following discussion – stressing "dementia" criteria factor – during FDA's Psychopharmacologic Drugs Advisory Cmte. meeting, Nov. 13-14. "***Dementia*** has been pasted into these (geriatric) guidelines," said cmte. discussant John Overall, PhD, ***UTex***. "I'm concerned about the use of dementia to be the disease with which all other manifestations we may want to treat in elderly people are associated with." He expressed a need to first examine and exclude the more traditionally known causes of mental deterioriation in the elderly such as hypoglycemia, cardiovascular problems or toxic conditions. Overall also questioned the test methods used for determining inclusion in a study of "demented" patients. He said there was an overemphasis on the Wexler Adult Intelligence Scale with its "rather outmoded deterioration quotient." Cmte. head Bonnie Camp, MD, PhD, followed up the cmte.'s vote with instructions to the FDA staff "to continue to work on the guidelines and to take the comments brought forward today and incorporate them in any changes."

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PARENTERAL DRUG ASSN. MEMBERS HAVE SUCCESSFULLY ARTICULATED TO FDA their interpretation of excessive specificity contained in planned Good Manufacturing Practice (GMP) regs for large volume parenteral drugs (LVPs), as proposed two years ago, FDA Com. Kennedy advised the group Nov. 16, during its NYC meeting ***(see related item T&G-7, this issue)***. FDA is aware of the damage to industry which could result from issuing "ice over" regs establishing procedures which could soon become obsolete, Kennedy said. The LVP GMPs, when finalized, will contain the "desired outcome," but will not be so specific as to preclude the use of different methods to achieve the standard, and guidelines will also be published which will describe current "state-of-the-art" procedures for achieving the outcome – but will be nonbinding, Kennedy continued. For example, Kennedy said, FDA will set out in the substantive LVP GMP document an acceptable "count" re room air sterility and then discuss in guidelines the best known method to achieve that count. "But, if someone comes up with a more cost effective method that is effective, we don't want to prohibit them from using it," he noted.

¶ FDA Associate Director for Compliance Theodore Byers told the PDA audience that the agency is currently "working actively on LVP GMP comments." He explained that FDA action on the LVP GMPs was interrupted because "among other things, the same people who work on the LVPs were given the job of writing the umbrella GMPs. . .We are going to develop a model plan for regulation of parenterals, meaning, at this point-in-time, *LVPs*." He added that a similar document for small volume parenterals would be developed in the future.

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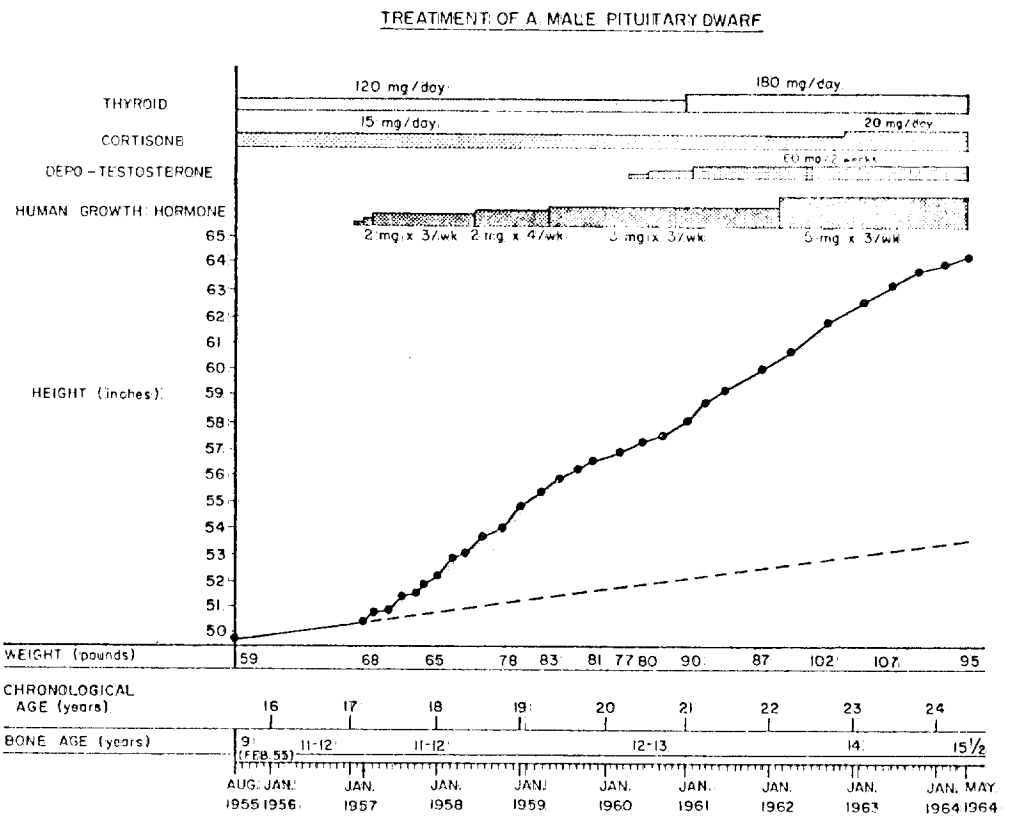

Figure 66-1. *Treatment of a patient with pituitary dwarfism with human growth hormone during replacement therapy with thyroid, cortisone, and testosterone.* (Modified from Raben, 1962b. Courtesy of the *New England Journal of Medicine.*)

To select those cases of short stature that are caused by deficient growth hormone, it is necessary to measure the growth hormone in the serum and to determine whether there is an appropriate response to a provocative stimulus. A requirement for therapy with growth hormone is based on the clinical findings and failure to respond to two or more provocative stimuli for secretion of the hormone. Once initiated, therapy should be evaluated for 8 to 12 months for the expected acceleration of growth. If therapy is successful, it should ideally be continued throughout childhood, and sex hormones, if needed, should be withheld until the possibilities of the response to growth hormone have been fully realized or until deemed necessary.

Undesirable side effects and complications are notably lacking; pain and swelling at sites of injection, allergic reactions, and chronic ill effects do not occur even when serum antibodies can be shown.

Human growth hormone is currently available in the United States only for treatment programs that include research efforts. It is obtained from the National Pituitary Agency of the National Institutes of Health, Bethesda, Maryland, upon approval of its Medical Advisory Committee. Hormone is supplied for a specific patient, and with yearly reapplication the supply is usually committed until the patient attains a height of 5 ft. It is estimated that the available supply of hormone is sufficient for treatment of only 10% of the hypopituitary children in the United States. All pathologists should cooperate by sending human pituitaries obtained at post-mortem examination to the National Pituitary Agency.

PROLACTIN

Despite a wealth of information about the nature and role of prolactin in a wide variety of species, unequivocal evidence for the existence of the hormone in man was obtained relatively recently (*see* Frantz *et al.*, 1972). It is now appreciated, however, that prolactin plays an important role in normal human function and in certain pathophysiological states.

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1974; Boston Collaborative Drug Surveillance Program, 1974; Heinonen *et al.*, 1974).

Ovary. The effects of prolactin on the ovary are species dependent. While the hormone has in the past also been referred to as *luteotropin*, this description was based on observations on rats and mice. In these species prolactin can prolong the life of the functioning corpus luteum, but it probably does not fulfill the role of a true luteotropic hormone. Notably, prolactin will not stimulate progesterone biosynthesis by corpora lutea from a variety of species, including rats (*see* Dorfman, 1972). It may, however, function to promote the luteal synthesis of cholesterol, the steroidal precursor. In contrast, luteinizing hormone is uniformly effective in stimulating progesterone synthesis. Surprisingly, recent evidence suggests that the sharp rise in prolactin secretion seen during proestrus in the rat may be responsible for luteolysis of corpora lutea formed during the previous cycle (Meites *et al.*, 1972).

Significant effects of prolactin on the human ovary are not known, and large variations of plasma prolactin concentrations are not apparent at different stages of the menstrual cycle.

Prolactin Secretion. Refined assay technics not only have been instrumental in the identification and purification of human prolactin but also have allowed exploration of physiological, pathological, and pharmacological influences on prolactin secretion (*see* Frantz *et al.*, 1972; Friesen, 1973).

The normal human plasma concentration of prolactin approximates 5 to 10 ng/ml and is essentially the same in males and females. Prolactin concentrations rise markedly during pregnancy, reaching a maximum at term. In nursing mothers prolactin secretion is critically controlled by the sucking stimulus or breast manipulation. Prolactin concentration can rise 10- to 100-fold within 30 minutes of stimulation. Other stimuli for prolactin secretion include psychic and physical stress, insulin-induced hypoglycemia, and high doses of estrogens. Interestingly, hypertonicity results in large elevations of plasma prolactin (Buckman and Peake, 1973). Future work should reveal whether any physiological significance is attached to this phenomenon or if it represents an undiscarded heritage of the *water-drive factor*.

Secretion of prolactin by the pituitary is under predominantly negative control by the hypothalamus. Thus, a prolactin release inhibiting hormone (PRIH) is secreted tonically by the hypothalamus and is carried by the hypothalamicoadenohypophyseal portal system to the adenohypophysis, where it inhibits prolactin secretion. There is considerable evidence that the release of PRIH is under adrenergic (dopaminergic) control, or that PRIH might even be dopamine (MacLeod and Lehmeyer, 1974). Thus, the administration of levodopa *in vivo* inhibits prolactin secretion, and dopamine is a highly effective inhibitor when instilled into the third ventricle or when applied to the isolated pituitary *in vitro*. Predictably, the phenothiazine and butyrophenone antipsychotics (*e.g.*, chlorpromazine, haloperidol), which are dopamine antagonists, enhance prolactin secretion, as can reserpine and α-methyldopa. The antipsychotic agents can cause significant galactorrhea associated with elevated plasma prolactin concentrations.

Functional disorders of the hypothalamus (Chiari-Frommel syndrome) and destructive or infiltrative disorders of the hypothalamus or pituitary stalk can also cause prolactin secretion and galactorrhea if there is interference with the tonic inhibitory hypothalamic influence. Pituitary oversecretion of prolactin, often due to functional tumors (Forbes-Albright syndrome), is also known. However, in none of these conditions is there strict correlation between plasma prolactin concentration and the presence or severity of galactorrhea.

Suppression of galactorrhea by administration of levodopa has been attempted with variable success (Turkington, 1972). Some patients who respond initially become refractory to the drug. More promising clinical results have been achieved with ergot derivatives (Floss *et al.*, 1973). Inhibition of lactation in women suffering from ergotism was observed centuries ago. This phenomenon has recently gained scientific credence with the discovery that ergot derivatives profoundly inhibit prolactin secretion *in vivo* and in isolated pituitary preparations *in vitro*. Since the inhibitory effect *in vitro* is antagonized by haloperidol, it is possible to hypothesize that ergot alkaloids activate the dopaminergic receptors that inhibit prolactin release. The experimental compound that has shown significant clinical promise is 2-bromo-α-ergokryptine. An additional finding of potential significance is that this compound can markedly suppress the growth of prolactin-secreting pituitary tumors (Quadri *et al.*, 1972).

Assays. The classical procedure for bioassay of prolactin is based on the original work of Riddle and associates (1933), namely, the increase in weight of the crop sacs of doves and pigeons. Other methods are based on the induction of secretory changes in the suitably prepared mammary glands of guinea pigs and rabbits. As mentioned above, radioimmunoassays have proven invaluable. A radioreceptor assay that utilizes a membrane receptor preparation isolated from rabbit mammary glands should also be useful to assess biological activity (Shiu *et al.*, 1973).

Human Placental Lactogen. Preparations from the human placenta contain growth-promoting and lactogenic activity (*see* Fukushima, 1961); Josimovich and MacLaren (1962) showed that such extracts cross-reacted with antisera to human growth hormone. Purified preparations caused a local response in the crop sac of the pigeon and maintained the function of the corpora lutea of rats but caused little

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Prolactin is widely distributed in the pituitaries of vertebrates; it has been found wherever sought in the pituitaries of mammals, birds, reptiles, and amphibia, and has been detected in a few species of fish. Among the amphibia, it has a clear-cut and very striking action in the newt *Triturus*, an action almost as remarkable as the metamorphic one of thyroid hormone on tadpoles. It transforms the terrestrial eft—a small, pink quadruped found under rocks in the woods—into a larger, dark-green, fish-shaped creature with a broad tail designed for swimming. The animal then takes to the water, its normal breeding habitat, which accounts for the term *water-drive factor* coined before the active principle was equated with prolactin (Bern and Nicoll, 1968).

The term *prolactin* was coined for the hormone responsible for the secretion of milk by the crop glands of the pigeon (Riddle *et al.*, 1933). In this bird there is a bilateral outpouching of the esophagus and, prompted by the psychological concomitants of brooding, a glandular structure grows within each pouch so that by the time of hatching a thick secretion, the crop milk, becomes available to each parent for regurgitating down the throats of the young. The response of the bird is a sensitive one; it is sufficient for one partner to see his mate sitting on the eggs for his pituitary to secrete prolactin and provoke the growth of the crop glands. In so naming the hormone, the tenuous analogy between the mammary gland and the crop sac was correctly drawn because it later was clear that prolactin is also of importance in initiating secretion from the breast.

Chemistry. The difficulty in isolating human prolactin is attributable to the facts that growth hormone is very similar in structure, possesses significant lactogenic activity in conventional bioassays for the hormone, and is present in human pituitaries in quantities far in excess of prolactin. However, refined bioassay technics permitted verification of the existence of human prolactin (Frantz and Kleinberg, 1970), and the technic of affinity chromatography permitted purification of a primate prolactin and subsequent development of a specific radioimmunoassay (Guyda and Friesen, 1971; Hwang *et al.*, 1971). Progress in the purification, chemistry, and physiology of human prolactin has been rapid since these advances.

Amino acid sequence determination of the amino-terminal region of the hormone (residues 1–50) has revealed approximately 25% identity and 50% homology with human growth hormone. There is high conservation of structure between human and ovine prolactin (80% identity), at least in this region, and the structure of the human hormone undoubtedly resembles closely that of sheep (Niall *et al.*, 1973).

Ovine prolactin has been characterized extensively, since the pituitaries of sheep are readily available and constitute a very rich source (Li *et al.*, 1970). The general structural features are very similar to those of the growth hormones (Table 66-1); the proposed evolutionary relationship of these molecules has been discussed above. As with the growth hormones, "isohormones" with presumed minor structural differences can be detected by electrophoresis.

Physiological Actions. *Breast.* The mammary gland is a site of immensely complex interactions among a number of hormones, with the majority of endocrine organs participating vigorously in the initiation and maintenance of lactation. The hormones of the adrenal cortex, thyroid, and ovaries are all necessary, and their presence is dependent on the trophic hormones of the adenohypophysis. Insulin and perhaps growth hormone exert important anabolic influences. The vital participation of prolactin completes the contribution of the anterior pituitary, with all of its major secretions at work. The role of oxytocin is considered in Chapter 42.

The actions of prolactin on the mammary gland have been studied particularly in explanted rodent tissue. However, investigations of normal and aberrant prolactin secretion seem to assure the existence of a comparable function in the human female. In systems *in vitro*, prolactin in the proper hormonal milieu can be shown to promote proliferation and subsequent differentiation of mammary ductal and alveolar epithelium. There is a rapid increase in RNA synthesis and induction of the synthesis of milk proteins and of enzymes necessary for lactose synthesis (Topper, 1970; Turkington *et al.*, 1973). At the subcellular level, activation of the development of rough endoplasmic reticulum, Golgi apparatus, and secretory granules is prominent.

These "mammotrophic" actions of prolactin suggest a possible role of prolactin in mammary tumorigenesis. Prolonged prolactin administration, the grafting of extra pituitaries, or experimental lesions in the median eminence that cause increased prolactin secretion all result in a high percentage of mammary tumors in susceptible rats and mice. Furthermore, estrogen will not produce tumors in the absence of the pituitary; however, in rats treated with carcinogens, prolactin promotes tumorigenesis in the absence of estrogens or progestins. Furthermore, drugs that enhance prolactin secretion (*e.g.*, reserpine, haloperidol—*see* below) facilitate experimental tumor growth, while those that inhibit secretion (*e.g.*, ergot derivatives) impede growth and reduce the incidence of spontaneous tumors in rodent models (*see* Meites *et al.*, 1972; McMahon *et al.*, 1973). Extrapolation between highly susceptible strains of rodents and man is obviously of questionable value, but these observations may provide additional explanations for the effectiveness of hormonal therapy of breast tumors. They may also relate to reports of the increased incidence of breast cancer among women who have been treated with reserpine for hypertension (*see* Armstrong *et al.*,

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growth in hypophysectomized animals; the active principle was named *placental lactogen*. Friesen (1965, 1966) purified the protein to homogeneity and demonstrated that it was strikingly lactogenic in pseudopregnant rabbits.

The chemical similarity of the substance to human growth hormone was shown by Sherwood (1967), and the complete amino acid sequence has been elucidated by Niall and associates (1971) and Li and coworkers (1973). The resemblance to growth hormone was amply confirmed by these studies, since both hormones contain 191 amino acids that differ in only 32 positions. The greater similarity of amino acid sequence in human placental lactogen and human growth hormone than in human and bovine growth hormones suggests a later evolutionary appearance of the placental lactogen. Its significance is, however, largely unknown. Because of its resemblance to growth hormone, the unwieldy name *chorionic somatomammotropin* is also in use.

GONADOTROPIC HORMONES

The pituitary gland plays an important part in the regulation of gonadal function throughout the vertebrate phylum, but the fullest understanding of the mechanisms involved has been achieved among the mammals. In this class there are striking species differences, with remarkable specialization in some as well as a certain uniformity among others, permitting the formulation of general principles. The adenohypophysis is physiologically and anatomically so situated that it can mediate neural messages that arise from the environment as well as intercept humoral signals from within. It can regulate such diverse phenomena as the annual growth and regression of the gonads of monestrous mammals in response to the changing length of daylight, the release of ova in the rabbit 10 hours after mating, and the reinitiation of follicular growth when a corpus luteum fails for lack of successful impregnation.

For over 40 years it has been known that two gonadotropins are involved, and it seems a general rule among mammals that follicular growth and development on the one hand and ovulation and the formation of a corpus luteum on the other are separately controlled. These same substances stimulate, respectively, the germinal elements of the testis and the androgen-secreting Leydig cells of the interstitial tissue. In the regulation of the function of the corpus luteum, several adaptations have arisen. In some species luteinizing hormone serves as the luteotropin, in others prolactin plays such a role, while in several species the uterus is somehow involved. During pregnancy the pituitary seems essential in some animals, while in most it is dispensable; luteal function may be autonomous, as in the herbivora, or regulated in part by a placental luteotropin, as in man.

Until very recently the functions of the gonadotropins in man were largely inferred from information derived from other mammals. Direct observations on human beings of the effects of gonadal hormones and their analogs and human gonadotropins have given better understanding and have opened new therapeutic approaches to the disturbances of human reproductive function.

Chemistry. The four gonadotropins considered here (two of pituitary and two of placental origin) are follicle-stimulating hormone (FSH), luteinizing hormone (LH), chorionic gonadotropin (CG), and the gonadotropin of pregnant mares' serum. The gonadotropins, with thyrotropin (TSH), constitute the glycoprotein group of hormones, and their similarities and general chemical features have been mentioned above (*see* Table 66-1).

Follicle-stimulating hormone (*FSH*) is the least well characterized of the pituitary hormones and the only one for which detailed information on amino acid sequence is not known. However, it is known that the human hormone consists of nonidentical, noncovalently linked subunits (Saxena and Rathnam, 1971). While the α subunit of FSH is significantly different from that of LH or TSH (Papkoff, 1972), there is evidence that the FSH α subunit can combine with the β subunit of chorionic gonadotropin with restoration of chorionic gonadotropin activity (Reichert, 1972).

Luteinizing hormone (*LH*), also called *interstitial cell-stimulating hormone*, more closely resembles TSH in its physical properties and chemical constitution than it does FSH. Ovine LH-α is identical to bovine TSH-α, and the β subunits show considerable homology. Considerable progress has been made with human LH, and the amino acid sequences of both α and β subunits have been reported (Sairam *et al.*, 1972; Shome and Parlow, 1973). Approximately 70% of the amino acid residues of both subunits are identical to the corresponding portions of the ovine hormone (Liu *et al.*, 1972a, 1972b). Many differences are explicable by a single DNA base change. Human LH-β is even more similar to a major portion of the β subunit of human chorionic gonadotropin, although the latter has a 30 amino acid carboxyl-terminal segment that is not present in human LH-β.

Human chorionic gonadotropin (*HCG*) is prepared

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GD6o (S) B16

PROLYLHYDROXYLASE
==========

Induction:

benzo(a)pyrene = 2-fold increase in neo-natal rat lung in organ culture (Hussain, M.Z. et al., Toxicology 12: 267-271, 1979)

not induced by non-carcinogenic pyrene (Hussain, M.Z. et al., Toxicology 12: 267-271, 1979)

Intracellular Localization:

ER-cisternae
O_2-exposure of lung cultures increases activity (Hussain, M.Z. et al., Toxicology 12: 267-271, 1979)

Function:

hydroxylation of Pro during collagen synthesis

activity usually correlates with tissues' potential for collagen synthesis (Hussain, M.Z. et al., Toxicology 12: 267-271, 1979)

Assay:

4-3HL-Pro + unhydroxylated collagen (Rapaka et al., BBA 429: 63, 1976)

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BIO-RAD Laboratories
CHEMICAL DIVISION

TECHNICAL BULLETIN

Protease
Detection Kit
April 1978

Protease Detection Kit

- **For detection of serum protease activity**
- **For quantitative estimation of proteolytic activities of trypsin, α-chymotrypsin, pronase and other proteolytic enzymes.**
- **For detection of contaminating protease activity in purified protein or nucleic acid preparations.**

The Bio-Rad Protease Detection Kit consists of 100 Substrate Gel Tablets, 10 polystyrene diffusion boxes, 2 vials of 5 ml each of a positive control serum containing plasminogen, urokinase and an instruction manual.

The determination of proteolytic activity is often estimated using protein substrates, requiring tedious acid precipitation and measurement of the absorbance of the acid-soluble fragments. With the continuing discovery of new types of proteases and the study of their biological properties, there is a need for convenient and sensitive assays for proteolytic activity.

Bio-Rad's Substrate Gel Tablets provide a rapid, convenient method for preparing agar diffusion plates for use in the detection of serum protease activity. The tablets produce a 1% agar gel containing a bovine casein preparation in a Tris buffered physiological saline solution at pH 7.2. Protease diffusion into the substrate gel is accompanied by digestion of the casein. This forms a transparent ring around the sample wells in a turbid gel. The size of the ring is a measure of the proteolytic activity of the sample.[1]

In addition, this method provides a sensitive assay for the detection of other proteases, such as trypsin, α-chymotrypsin and pronase. Figure 1 shows the diffusion pattern observed using several trypsin concentrations. Similar patterns were obtained for α-chymotrypsin and pronase. The sensitivity of this assay using trypsin is similar to that reported by Sevier,[2] using ^{125}I labeled solid phase protein substrates, but the Bio-Rad protease assay is more convenient and does not require the preparation of radioactive substrates.

Applications

Figure 2 illustrates the relationship between the ring diameter and the logarithm of the trypsin concentration applied to the gel.

A quantitative determination of the concentration of trypsin could thus be obtained for samples containing from 2.5 to 20 μg trypsin/ml solution. Trypsin activity could also be detected for samples containing from 0.5 to 1.0 μg trypsin/ml, although the relationship of ring diameter to the logarithm of trypsin concentration was not linear for this lower concentration range.

Using this assay, protease activity has been detected in commercial preparations of neuraminidase and rabbit antisera directed against human serum proteins. Proteolytic activity was detected in both partially and highly purified preparations of *Clostridium perfringens* neuraminidase from two suppliers (Figure 3). This assay, therefore, should provide a convenient and sensitive method for detection of the contamination or removal of proteolytic activity from neuraminidase, for use in the study of cell surfaces or the function of glycoproteins.

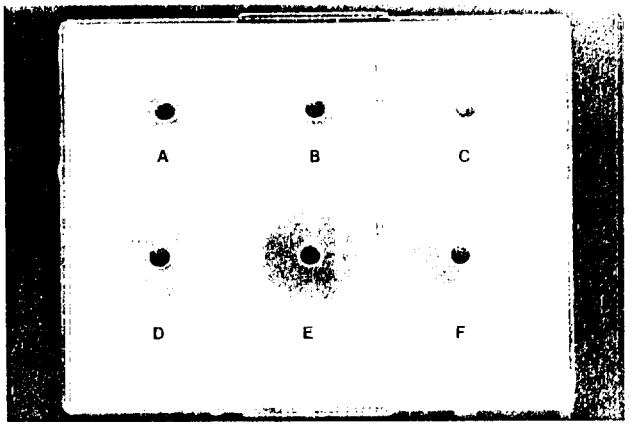

Fig. 1. Determination of trypsin activity. Aliquots (20 μl) of trypsin solutions in 0.05M Tris-HCl, pH 7.5, .05M $CaCl_2$, containing 0.5 (A), 1.0 (B), 2.5 (C), 5.0 (D), 10 (E) and 20 μg trypsin/ml (F) were incubated for 24 hours at 22°C and overlayed with 3% acetic acid.

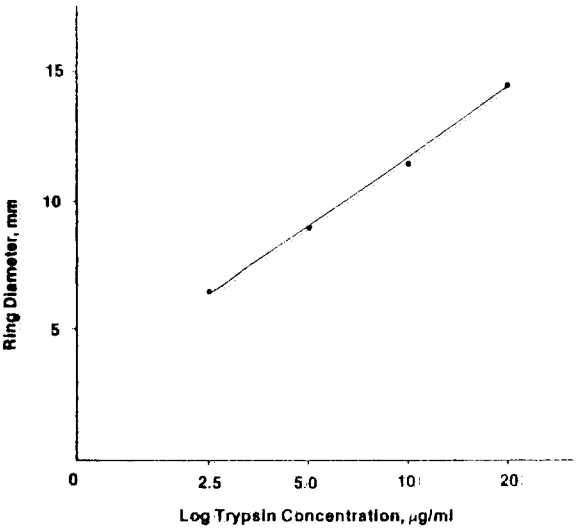

Fig. 2. Relationship of ring diameter to trypsin concentration. Aliquots (15 μl) of trypsin solutions containing from 2.5 to 20 μg trypsin/ml 0.05M Tris-HCl pH 7.5, .05M $CaCl_2$ were incubated for 24 hours at 22°C. The gels were overlayed with 3% acetic acid and the ring diameters were measured. The specific activity of the trypsin was 3.3 μmoles/min/mg using N-benzoyl-DL-arginine-p-nitroanilide HCl (BAPNA).[3]

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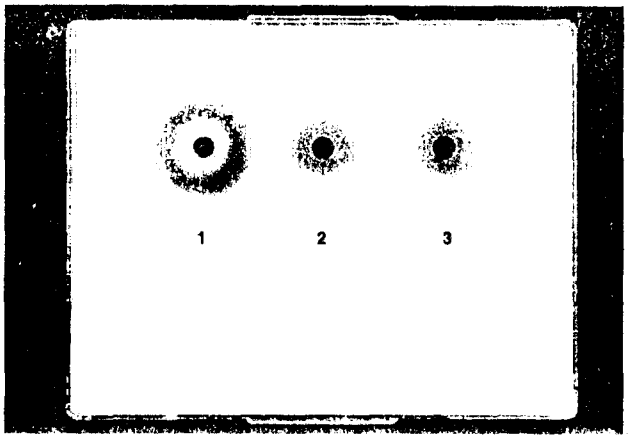

Fig. 3. Protease activity of commercially available neuraminidase preparations. Aliquots of neuraminidase solutions (25 µl) in 0.01M K_2HPO_4, pH 7.25, 0.15M NaCl were incubated for 24 hours at 22°C and overlayed with 3% acetic acid. Sample 1: partially purified neuraminidase (1.51 units/mg protein) containing 15 units/ml; Sample 2: highly purified neuraminidase (28 units/mg protein) containing 20 units/ml; Sample 3: highly purified neuraminidase (11.9 units/mg) containing 11.9 units/ml.

Procedure for Activation of Serum Plasminogen with Urokinase*

1. Dissolve the urokinase sample in 0.01M K_2HPO_4, pH 7.25, containing 0.15M NaCl and 1 mg bovine serum albumin/ml to give a solution containing 300 to 500 Ploug units/ml.
2. Combine 15 µl of urokinase solution with 15 µl of serum sample and let stand 30 minutes at 20-25°C.
3. Apply 5 to 25 µl of the urokinase-treated sample to a protease detection gel prepared according to steps 1-4 in the "Procedure for Protease Detection" section. Also apply separately an untreated aliquot of the serum to determine the amount of endogenous plasmin present in the serum.
4. Incubate the gel 16 to 24 hours at 20-25°C, and terminate the plasmin activity by overlaying the gel with 3% acetic acid for 10 minutes.
5. Rinse the gel with water and measure the diameter of the rings.

* Most sera show proteolytic activity only after incubation with urokinase, an enzyme known to convert plasminogen to plasmin.

Procedure for Protease Detection

1. Place two Substrate Gel Tablets in an 18 × 150 mm test tube and add 10 ml water. Allow the tablets to hydrate for 15 minutes at room temperature, then vortex the mixture thoroughly to obtain complete suspension of the tablets. Failure to adequately solubilize the substrate (casein) and buffer components before heating will result in a heterogeneous plate.
2. Heat the suspension in a boiling water bath until the agar dissolves completely (3 to 5 minutes). Vortex the solution and visually check that all solids have dissolved. (Note: Safety glasses should be worn when vortexing to avoid injury if the heated agar is spilled during mixing. The mouth of the tube should be tilted slightly away from the user during vortexing.) Do not overheat the agar; melt once the casein has dissolved, as prolonged heating can result in precipitation of the casein. Cool to about 55°C.
3. Carefully pipet the hot agar melt onto a plastic diffusion plate, and allow the solution to cool undisturbed to room temperature.
4. After the gel has set and cooled to room temperature, punch 2.0 to 4.0 mm diameter sample wells in the gel.
5. Using a micropipet, fill the sample wells with 5 to 15 µl of sample.
6. Incubate the plates at 20-25°C for 16 to 24 hours. (Incubation time may be lengthened for increased sensitivity. Alternatively, the substrate tablets can be dissolved in 15 ml water to produce a thicker gel, which can accept sample volumes of 25 µl per well.)
7. Termination of the protease digestion and enhancement of the rings is accomplished by overlaying the plate with a solution of 3% (v/v) acetic acid. After 10 minutes the plate can be rinsed with water and the diameter of the rings measured. Qualitative protease detection may not require fixing.

References

1. This assay is an adaptation of that described by Bjerrum, O.J., et al., in "Quantitative Immunoelectrophoresis," *Scandinavian J. Immunology*, Supplement 2, N.H. Axelsen, ed., Aas and Wahl, Oslo, Norway, 1975, pp. 82-83.
2. Sevier, E.D., *Anal. Biochem.*, 74, 592 (1976).
3. Preiser, H., Schmitz, J., Maestracci, D., and Crane, R.K., *Clin. Chim. Acta*, 59, 169 (1975).

Ordering Information

Catalog Number	Product Description	
⊗ 500-0010	**Protease Detection Kit,** sufficient for at least 500 detections or 250 quantitative determinations.	44.–
⊗ 500-0003	**Urokinase,** 1,000 Ploug units, sufficient for 250 plasminogen detections.	51.–
170-4029	**Gel Puncher,** 4 mm diameter	
170-4030	**Gel Puncher Set,** 1 each of 2, 2.5, 3 and 4 mm diameters	

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GD55 (S) B26 (LA) 12.May.81

PROTEASE INHIBITORS
==========

Bronchus Mucus:

antileucoprotease (cf.) :
identical with human seminal or cervix uteri secretion inhibitor.

function: protection of cilia,
specificity: cf. "antileucoprotease"
(Laurell, C.-B., plenary lec., Congr. Scand. Ger. Soc. Clin. Chem., Hamburg, Oct. 198o+)

Serum:

(Laurell, C.-B., plenary lec., Congr. Scand. Ger. Soc. Clin. Chem., Hamburg, Oct. 198o+)

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GD61 (S) B13

PULMONARY DISEASES
==========

Pneumoconiosis
Sarcoidosis (parenchymal)
Fibrosing alveolitis
Asthma
Alveolar proteinosis

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PULMONARY SECRETIONS

Causes of Surfactant Deficiencies:

ingestion of paraquat,
administration of fluorocarbons,
oxygen exposure,
cigarette smoke,
petrol vapour
= respiratory distress syndrome (important cause of neonatal death in developed countries) (Le Mesurier, S.M. et al., Pathology 11: 81-87, 1979)+

Albumin:

may represent approx. 3o o/o of total lavaged protein in sheep (Lemaire, I., Sirois, P., Rola-Pleszczynski, M., Massé, S. and Bégin, R., Early biochemical reactions in the lung of sheep exposed to asbestos: evidence for cyclic AMP accumulation in broncho-alveolar lavage fluids, Lung 159: 323-332, 1981)

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PURITY
======

Criteria.

melting point
thin-layer chromatography
UV and fluorescence spectroscopy
mass spectrometry

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PUTRESCINE (1)
==========

1,4-diamino butane

Biosynthesis:

from ornithine by decarboxylation, during fermentation of meat by microorganisms

Occurence:

ribosomes,
bacteria,
feces

Toxicity:

non-toxic

Determination:

HPLC: cf. POLYAMINES

extraction from epidermis and determination:

homogenization of pooled epidermis (4 mice) in o.2 mol/l perchloric acid acc. to Inoue and Mizutani (Anal Biochem. 56: 56: 4o8, 1973), chromatography of extract on Dowex AG 5o W, dansylation, TLC, assay by fluorescence (exi: 36o nm, emi: 5oo nm) (Marks, F. et al., Cancer Research 39: 4183-4188, 1979+)

Content of Biological Samples:

urine: 4,o.5 and 2 nmol/ml putrescine, cadaverine or spermidine (hu)

serum: o.2, o.o2 and o.2 nmol/ml putrescine, cadaverine or spermidine

liver: 6, o, 1ooo and 6oo nmol/g WW putrescine, cadaverine, spermidine and spermine (Samejima et al., Anal. Biochem. 76: 392-4o6, 1979+) (rt)

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GD6o (S) B1o

PYRENE
======

not carcinogenic PHC (Casto et al., Eds., Chemical carcinogenesis, Part B, Marcel Bekker, New York, 1974, p. 6o7)

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PYRIDOXAL 5'-PHOSPHATE

Determination:

(A) indirect analysis by PLP-dependent apoenzymes: extremly sensitive, not suitable for routine, subject to inferference

(B) Fluorometry:

(a) KCN-method = 4-pyridoxic acid 5'-phosphate requires preparative ion-exchange chromatography for removal of interfering compounds.

(b) semicarbazide-method
= PLP-semicarbazone, fluorometic detection after HPLC. Suitable for animal tissue perchloric acid extracts

(Gregory III, J.F., Analyt. Biochem. 1o2: 374-379, 198o)#

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GD27 (S) B29 (PW)

PYRUVIC ACID
==========

Increased blood level:

liver disease
congestive heart failure
diabetes
thiamine deficiency
neoplasia

Stability:

immediate precipitation of blood proteins compulsory, blood rather than serum more suitable for precipitation with 6 o/o perchloric acid.

Per-supernatant: stable for .GT. 1 month at 3 degrees centigrade (Sigma Technical Bulletin No. 726, 1977+)

Normal range:

o.o3 to o.o8 mmol/l, fasting venous blood (increase during exercise) (Sigma Technical Bulletin No. 726, 1977+)

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QUALITY ASSURANCE
==========

(1) Mitteilung über Versuchsbeginn:

HEt, QA

(2) Analyse der Prüfsubstanz-konz. im Applikationsgemisch:

unbedingt notwendig

(3) Unterschrift unter Rohdaten:

Laborant, weitere Unterschriften (z.B. Laborleiter) sind interne Zusatzregelungen

(4) Haltbarkeit von Reagenzien:

auf jeder Flasche/Gefäß angeben

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QUARZ
=====

Action on Alveolar Macrophages:

no stimulation of prolonged lymphocyte binding as observed with Asbestos (cf.) (Miller, K., personal commun., Nov. 81)

Chronic Toxicity/Carcinogenicity:

50 mg/m3, 6 h/d, 5 d/w, 24 months (rt)
F-344 rats:
dramatically reduced survival time
epidermoid carcinomas
(Wehner, A.P., Dagle, G.E., Clark, M.L., Buschbom, R.L., Lung changes in rats following inhalation exposure to volcanic ash for two years, Environ. Res. 40 : 499-517 (1986)

Lung Cancer Risk:

Epidemiology: (hu)
(Goldsmith, D.F., Guidotti, T.L., Johnston, D.R., Does occupational exposure to silica cause lung cancer?, Amer. J. Ind. Med. 3 : 423-440, 1982)

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RACHENABSTRICHE
==========

Vorherrschende Spezies:

Neisseria
Streptokokken, nicht-hämolysierend

Sonstige Spezies:

Staphylokokken
Coliforme Bakt.
Hämophilus hemolyticus

Akute Infektion des Respirationsstrakts:

z.B. Streptokokken, hämolysierend (Pike, R.M., Am. J. Hygr. 41: 211-22o, 1945)

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GD27 (S) B8 (PW)

RADIOCHEMICAL PURITY

Determination:

TLC not sufficient, HPLC required: cf. dibenzanthracene

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RADIO-IODINATION
==========

Iodination of Proteins:

Iodine is incorporated into Tyr-residues.

Methods:
(1) Chloramine-T
(2) Lactoperoxidase: enzymic oxidation milder than Chloramine-T
(3) Acylation:
Active acylated reagent is iodinated by Chloramine-T method and then coupled to protein via its free amino-groups. (Jeffcoat, S.L. in: Gupta, D. (Ed.): Radio-Immunoassay of Steroid Hormones, Weinheim: Verlag Chemie, 1975, pp. 185-195)+

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Source: https://www.industrydocuments.ucsf.edu/docs/rkdl0000

RAYNAUD SYNDROME

Symptoms:

convulsions of arteries, mostly of fingers as secondary result of other disease

may occur in vinyl chloride intoxication

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GD27 (S) A18 (PW)

RECOVERY
========

$$\frac{\text{(Conc. (sample + standard) - Conc. (sample)}}{\text{Conc. Standard}}$$

x 1oo = recovery (o/o)

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GD59 (S) B22

RESPIRATORY DISTRESS SYNDROM
==========

inadequate production of surface active material in fetal lung --- oxidative stess in premature infant (Tanswell, K.A., Smith, B.T., Pediat. Res. 13 : 1097-1100, 1979)

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Source: https://www.industrydocuments.ucsf.edu/docs/rkdl0000

RESPIRATORY EPITHELIUM (1)

Composition (Cell Types):

pseudostratified ciliated, with goblet cells and basal cells

Carcinogenicity:

main target in respiratory tract

Species differences:

OCC. OF EPITHELIUM	MAN	RAT	MOUSE
trachea	+	+	+
main bronchi	+	+	o
segmental bronchi	+	+	o
subsegmental bronchi	+	o	o

(Reznik-Schüller, H.M., "Wissenschaftliches Kolloquium", Aug. 21, 1980)

Ultrastructure:

human and rodents very similar

(1) Ciliated cells:

Typical appearance of normal cells of respiratory epithelia: Long axis perpendicular to basal membrane (polarity), few mintochondria, ER and polyribosomes, few cytochrome P-450 (human)(Reznik-Schüller, H.M., "Wissenschaftliches Kolloquium", Aug. 21, 1980)

(2) Mucus cells:

humans: vesicles fill cytoplasm, main occurence of P-450

rodents:
less vesicles, less P-450 but more ER as compared to human

(3) Basal cells:

metabolically inactive, big nucleus; stem cell for other resp. epithelial cells (Reznik-Schüller, H.M., "Wissenschaftliches Kolloquium", Aug. 21, 1980)

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RESPIRATORY EPITHELIUM (2)

(4) Clara cells:

Occurence in regions which lack basal cells (e.g. human alveoli)
Also stem cells for other epithelial cell types,
highest activity of monooxygenases,
very high content of smooth ER in syr. hamster (peculiarity)
(Reznik-Schüller, H.M., "Wissenschaftliches Kolloquium", Aug. 21, 1980)

(5) APUD-cells:

Amine precursor uptake, dehydrogenizing
function unknown
source for oatcell carcinoma (2nd position in frequency of human lung carcinoma, not inducible in animals) (Reznik-Schüller, H.M., "Wissenschaftliches Kolloquium", Aug. 21, 1980)

(6) Alveolar cells (pneumocytes):

lamellar bodies

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RETINOL
=======

SCE:

No induction in V79 cells without and with S9

Induction of SCE by cyclophosphamide and aflatoxin B1 inhibited. Effect indicates interaction with metabolic activation system.

Certain retinoids

in vivo
- prevent or delay cancer induction
- reverse premalignant changes

in vitro
- inhibit growth of tumor cell lines
- suppress transformation
- antagonize effects of tumor promoters

(Huang, C.C., Hsueh, J.L., Chen, H.H. and Batt, T.R., Retinol (vitamin A) inhibits sister chromatid exchanges and cell cycle delay induced by cyclophosphamide and aflatoxin B1 in Chinese hamster V79 cells, Carcinogenesis 3: 1-5, 1982+)

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RNA
===

Epidermal RNA Synthesis:

Whole smoke condensate and hexamic fractions inhibitory 4 and 2 h after a single dermal application, increase (2 to 3 fold) relative to acetone control thereafter. Viscous WSC appeared to penetrate slower than hexanic fraction. (mu)
(Alexandrov,K. and Vendrely, C., Chem. Biol. Interactions 4: 155-161,1971/72+)

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GD61 (S) B25

SACCHARIN
=========

Metabol. Cooperation:

positive = promoting activity (Trosko et al., Nature 285: 1o9, 198o)

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Source: https://www.industrydocuments.ucsf.edu/docs/rkdl0000

GD55 (S) A23

SALICYLAMIDE
==========

inhibition of phase 2 reactions, 2oo micromol/l, rat hepatocytes (Orrenius, S., Joint Meeting, Sep.8o, Lübeck-Travemünde)+

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Source: https://www.industrydocuments.ucsf.edu/docs/rkdl0000

GD58 (S) B3o

SALIVA
======

Plasma Protein Content:

low conc. of albumin,
IgA,
haptoglobin (traces)
(Ryley and Brogan, Brit. J. Exp. Pathol. 49 : 625, 1968)

Protein Content:

human:
similar to sol phase of sputum (=), low protein concentration
(Ryley, H.C., Biochim. Biophys. Acta 271: 3oo-3o9, 1972)+

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Source: https://www.industrydocuments.ucsf.edu/docs/rkdl0000

SELENIUM

Determination in Serum:

TLC approx. 1o x more sensitive than AAS (Seminar TLC/HPTLC, Essen, Dez. 1979, lecture Trampisch)

Carcinogenicity/Toxicity:

Inorganic selenium derivatives are extremely hepatotoxic but do not appear to be carcinogenic. In some cases inhibition of the carcinogenicity or mutagenicity of other substances has been observed. (CaD., p. 107)

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Source: https://www.industrydocuments.ucsf.edu/docs/rkdl0000

SEROTONIN
=========

Appetite Regulation:

Serotonin-containing neurons involved in control of appetite for carbohydrates (Wurtman, J., Intern. J. Obesity 4: 31o-313, 198o+)

incr ease of carbohydrates
incr release of serotonin in brain
incr carbohydrates appetite
eased

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Source: https://www.industrydocuments.ucsf.edu/docs/rkdl0000

SEX DIFFERENCES
==========

- parathion approx. 2x as toxic to female as compared to male rats. Effect due to greater P-450-MFO (detoxifying parathion) in males.

- greater P-450-MFO activity in male rat appears to be androgen related: castration or estrogen treatment of males or testosterone treatment of females decreases sex difference

- sex differences in metabolism more frequent in rats than in other species

(CaD, 67)

- hexobarbital-induced sleeping time longer in female than in male rats

- glucuronidation greater in male rats

- aniline hydroxylation, however, show little sex differences in the rat

- renal toxicity of chloroform more severe in male mice

(Timbrell, 1982, LI: TOX 95)

MFO:

C3H/He mice, liver: (mu)

quotient male/female:

AHM:	0.3
NADPH-cytochrome C reductase:	0.75
cytochrome P-450:	1.24 (!) (similar in BALB/CJ mice)

Effect of sex hormones on gonadectomiced mice:

estradiol: increase in females, not in males

testosterone: decrease in both sexes

therefore testosterone may regulate decrease in males
(Watanabe et al. (1980) L3/L13)

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Source: https://www.industrydocuments.ucsf.edu/docs/rkdl0000

GD57 (S) A19

SIALIC ACID
==========

Assay:

analysis for both free and bound sialic acid (Downs, Pigman in: Whistler, BeMiller (Eds.): Methods in carbohydrate chemistry, Academic Press, New York, Vol. 7, 1976, pp.233)

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Source: https://www.industrydocuments.ucsf.edu/docs/rkdl0000

SKELETTMUSKEL
==========

Muskelkonzentration von Metaboliten:

$$C_{mw} = \frac{C_m - (o.o5 \times C_b + o.15\ C_{pw})}{o.6}$$

C_{mw} = Conc. in muscle water (micromoles/l)

C_m = Conc. in muscle (nmoles/g)

C_b = Conc. in blood (nmoles/ml)

C_{pw} = Conc. in plasma water = $C_p/o.93$
(plasma: 93 o/o water)

muscle: 8o o/o water
(6o o/o intracellular,
15 o/o interstitial,
5 o/o intravascular)

(Ruderman, N.B. et al., Am. J. Physiol. 233: 1o9-114, 1977)

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Source: https://www.industrydocuments.ucsf.edu/docs/rkdl0000

SKELETAL MUSCLE

Blood Flow:

increase during exercise (Schultz, Th.A. et al., Am. J. Physiol. 233 (6) : 514-518, 1977)

Isolated Muscle:

red and white rat adductor muscle fibres (Beatty et al., Am. J. Physiol. 2o4: 939, 1963)

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Source: https://www.industrydocuments.ucsf.edu/docs/rkdl0000

SLOW REACTING SUBSTANCE OF ANAPHYLAXIS (SRS-A)

release from lung cells (pig) during treatment with ionophore A 23187.
Released SRS inactivated in presence of alveolar macrophages. (Paterson, N.A.M., Craig, I.D. Amer. Rev. Resp. Dis. 119: 76, 1979)

components of SRS-A:
leukotrienes C4, D4 and E4

C4: 5-OH-6-glutathionyl-7,9-trans-11,14-cis-icosatetraenoic acid
D4: 6-sulfidocysteinylglycine
E4: 6-sulfidocysteine

Determination:

Detection limits:

HPLC + RIA: o.2 ng (Levine, L., Morgan, R.A., Lewis, R.A., Austen, K.F., Clark, D.A., Marfat, A. and Corey, E.J., Radioimmunoassay of the leukotrienes of slow reacting substance of anaphylaxis, Proc. Natl. Acad. Sci. 78: 7692-7696, 1981)+
HPLC + bioassay: 1 to 1o ng (Lewis et al., PNAS 77, 371o-3714 (8o))
HPLC + A28o: 25 to 3o ng
Ria: comparable affinities for leucotrienes C4, D4 and E4

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Source: https://www.industrydocuments.ucsf.edu/docs/rkdl0000

GD57 (S) B2o

SODIUM
======

Determination by Flame Photometry:

serum/plasma: protein interference possible, dependent upon atomizer, sodium value slightly reduced, check with and without precipitation (Bergström, J., Scand. J. clin. lab. Invest. 68: 14-17, 38-41, 43, 74-75, 1962)+

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Source: https://www.industrydocuments.ucsf.edu/docs/rkdl0000

SODIUM AZIDE
==========

Ames Test:

positive with TA1535 and TA1oo.
good dose-response in o.3 to 1oo microgram/plate-range (Dunkel, J. Assoc. Off. Anal. Chem. 62: 874-882, 1979)+

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Source: https://www.industrydocuments.ucsf.edu/docs/rkdl0000

SPECIES DIFFERENCES (1)
==========

Syrian hamster differs markedly from mice, rats and dogs in its response to lung irritants and carcinogens.

- resistance to NO2 irritation (lower resp. tract):
  hm .GT.rat, mu, hu

- resistance to nicotine effects:
  hm .GT.mu, rt: nicotine i. p. and inhalation of smoke, differences in acute toxicity as measured by LD50 and mean survival times, respectively
(Bernfeld and Homburger, Toxicol. Appl. Pharmacol. 22 : 324-325 (1972))

- incidence and morphology of tumors induced by chemical carcinogens

- resistance to DENA (systemic) carcinogenesis (nasal, tracheal, lung tumors):
  mice .GT.rat .GT.hm

- resistance of tracheal mucosa to chemical carcinogens:
  mu, rt .GT.hm

- resistance to tumor development in broncho-alveolar region:
  hm .GT.rt, mu
(Kennedy and Little in: Homburger (ed.), The Syrian hamster in toxicology and carcinogenesis research, Basel: S. Karger, Vol. 24, 1979, pp. 302-314)

- bactericidal activity of alveolar macrophages: rabbit macrophages avidly ingest and kill St. aureus, whereas macrophages from rats ingest but poorly kill the bacterium (rb rt)

- tracheal mucus velocity varies with species

- oxygen tolerance (= SOD inducibility) present in rat but not in guinea pig, hamster or mouse

- toxicity of alpha-naphtylthiourea, paraquat, 4-ipomeanol varies with species

- significant interspecies differences in the fine structure of the respiratory tract. Rats: no well-developed respiratory bronchioles, simple pulmonary acimus, terminal bronchioles open into alveolar ducts. (rt

- rat develop lesions in terminal bronchioles after exposure to ozone but monkeys have lesions in respiratory bronchioles
(Brain, J.D. and Mensah, G.A., Am. Rev. Resp. Dis. 128: S87-S90 (1983) L24)

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Source: https://www.industrydocuments.ucsf.edu/docs/rkdl0000

SPECIES DIFFERENCES (2)
==========

- mouse but not rat can hydroxylate biphenyl at the 2 position (P-450-dependent monooxygenase) (mu)
- arylacetic acids predominantly conjugated with glutamine or glycine in man or rat, respectively (hu, rt)
- very little glucuronidation in the cat
- no conjugation with sulfate in the pig (pg)

(CaD, 67)

- guinea pig bile contains little or no cholic acid (Hansma and Ostwald (1974) L84/B7) (gp)
- hamster less sensitive to tumorigenicity of diluted diesel exhaust than rats and mice (hm, rt, mu)

(Heinrich, U., Pott, F., Mohr, U., Experimental lung tumors after inhalation of emissions of pyrolized pitch and Diesel engine, The Toxicologist, Abstract of the 25th Anniversary Meeting, vol. 6 (1), March 1986)

Skin Painting:

Mouse and rabbit, but not rat (?) and guinea pig are particularly sensitive to PAH carcinogens.
sources: PAH penetration, pattern of hair growth, metabolism
(Schmeltz (1972) LI-Code: TOB 14)

Hair Growth:

synchronous: mouse, rat, hamster, rabbit
asynchronous: man, guinea pig, cat
(Schmeltz (1972) LI-Code: TOB 14)

O^6-AG Repair:

organs of hamsters generally less active than those of rats (Margison, G.P., Margison, J.M., Montesano, R., Methylated purines in the deoxyribonucleic acid of various Syrian golden hamster tissues after administration of hepatocarcinogenic doses of dimethylnitrosamine, Biochem. J. 151 : 627-634 (1976), Becker, R.A., Shank, R.C., Kinetics of formation and persistence of ethylguanines in DNA of rats and hamsters treated with diethylnitrosamine, Cancer Res. 45 : 2076-2084 (1985)

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Source: https://www.industrydocuments.ucsf.edu/docs/rkdl0000

SPECIES DIFFERENCES (3)

Species Defects in Common Metabolic Reactions:

SPECIES	DEFECTIVE REACTION
rat	N-hydroxylation of aliphatic amines
dog	acetylation of primary arylamino groups
cat	glucuronide formation
guinea pig	mercapturic acid formation
pig	sulfate formation

from: Kramer, M., Eckert, H.G., The changing face of technology and its likely impact on the practice of toxicology, in: Hodel, C.M. (Ed.): FEST Federation of European Societies of Toxicology, 1986, pp. 11-13

Drug Metabolism:

In the rat the metabolism is totally different from man for approx. 40 0/0 of the studied drugs.
(Kramer, M., Eckert, H.G., The changing face of technology and its likely impact on the practice of toxicology, in: Hodel, C.M. (Ed.): FEST Federation of European Societies of Toxicology, 1986, pp. 11-13)

Skin Sensitivity to Ionizing Radiation:

single local beta-irradiation produces tumors of hair follicle cell origin at a high frequency in rat but not in mouse skin (Albert, R.E., Burns, F.J., Bennett, P., Radiation-induced hair-follicle damage and tumor formation in mouse and rat skin, J. Natl. Cancer Inst. 49 : 1131-1137 (1972))

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SPERMINE (1)

Determination:

HPLC: cf. POLYAMINES

Extraction from Epidermis and Determination:

homogenization of pooled epidermis (4 mice) in o.2 mol/l perchloric acid acc. to Inoue and Mizutani (Anal. Biochem. 56: 4o8, 1973), chromatography of extract on Dowex AG 5o W, dansylation, TLC, assay by fluorescence (exi: 36o nm, emi: 5oo nm) (Marks, F. et al., Cancer Research 39: 4183-4188, 1979+)

Content of Biological Samples:

urine: 4,o.5 and 2 nmol/ml putrescine, cadaverine or spermidine (hu)

serum: o.2, o.o2 and o.2 nmol/ml putrescine, cadaverine or spermidine (hu)

liver: 6, o, 1ooo and 6oo nmol/g WW putrescine, cadaverine, spermidine and spermine (Samejima et al., Anal. Biochem. 76: 392-4o6,.1976+) (rt)

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SPUTUM
======

Separation of Sol- and Gel-Phase:

ultracentrifugation, 120000 x g, 4 h (Ryley, H.C., Biochim. Biophys. Acta 271: 300-309, 1972)+

Preparation of Antiserum against Secretory Sputum Proteins:

increase of specificity by treatment with serum immunoabsorbent: = 14 precipitates (Ryley, H.C., Biochim. Biophys. Acta 271: 300-309, 1972)+

Protein Content:

human:

13 protein precipitates with antiserum,
lactoferrin,
secretory IgA,
amylase,
lysozyme,
a macroglycoprotein,
a calcium-precipitable protein ,
hydroperoxidase
(Ryley, H.C., Biochim. Biophys. Acta 271: 300-309, 1972)+

Composition:

water (95 0/0),
amino acids,
low-MW-carbohydrates,
high-MW-glycoproteins,
lysozyme,
lactoferrin,
IgA,
IgG,
albumin,
transferrin,
alpha-1-antitrypsin,
fibrinogen,
ceruloplasmin
(Last, J.A., Mucus production and the ciliary escalator, in: Witschi, H. and Nettesheim, P.: Mechanisms in Respiratory Toxicology, Vol. 1, Boca Raton, Florida, USA, CRC Press, Inc., 1982, pp. 248-249)

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Source: https://www.industrydocuments.ucsf.edu/docs/rkdl0000

GD56 (S) B22

SQUAMOUS CARCINOMA
==========

Description:

squamous (schuppiges) type of tumor

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SUBSTANCE P
==========

Chemical Composition:

undecapeptide (11AA), similar to VIP, somatostatin and bombesin

Function:

neurotransmitter, released from C-fibre afferents (neurons) in nasal mucosa, trachea and skin. Causes local vasodilatation and edema
(Lundblad, L., Hua, X.Y., Lundberg, J.M., Mechanisms for reflexive hypertension induced by local application of capsaicin and nicotine to the nasal mucosa, Acta Physiol. Scand. 121 : 277-282 (1984))

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SYMPATHOMIMETIKA

Überwiegend an β-Rezeptoren wirksame Sympathomimetika

Substanzen

Neben den „klassischen" β-Sympathomimetika Isoprenalin (N-Isopropyl-Noradrenalin) und Orciprenalin (dem 3,5-Dihydroxy-Analogen des Isoprenalin), die gleichermaßen β_1- und β_2-Rezeptoren (vgl. Tab. 2) stimulieren, ist eine Reihe von Substanzen synthetisiert worden, die bevorzugt an β_2-Rezeptoren wirksam sind (Fenoterol, Terbutalin, Salbutamol, Abb. 12 unten). Mit Ausnahme des Katecholamins Isoprenalin sind die β-Sympathomimetika 3,5-Dihydroxyphenyl-Derivate (Orciprenalin, Terbutalin, Fenoterol) oder tragen einen CH_2OH-Substituenten anstelle der 3-OH-Gruppe (Salbutamol). Sie werden durch die COMT (z. B. in der Leber) nicht abgebaut und sind daher nach oraler Verabfolgung besser wirksam und haben eine längere Wirkdauer (bis 6 Std.) als Isoprenalin (ca. 3 Std.) (vgl. S. 127).

Wirkungen auf β_1- und β_2-Rezeptoren

β-Sympathomimetika haben am Herzen eine positiv chronotrope, inotrope und dromotrope Wirkung – d. h. sie führen über die Erregung der β_1-Rezeptoren des Herzens zu Steigerung der Frequenz, der Kontraktionskraft und der Überleitungsgeschwindigkeit (und damit auch zu einem erhöhten Sauerstoffverbrauch). Die periphere Vasodilatation als β_2-Wirkung senkt den Kreislaufwiderstand. Erschlaffung der glatten Muskulatur der Bronchien („Bronchospasmolyse") und – vor allem des graviden – Uterus („Tokolyse") sind ebenfalls β_2-sympathomimetische Wirkungen (Tab. 2). Die Wirkungen von β-Sympathomimetika am Herzen und an den Bronchiolen sind in Abb. 12 schematisch charakterisiert. Nach neueren Untersuchungen soll auch Adrenalin vor allem an β_2-Rezeptoren ($\beta_2 > \beta_1$), Noradrenalin dagegen überwiegend an β_1-Rezeptoren ($\beta_1 > \beta_2$) wirksam sein.

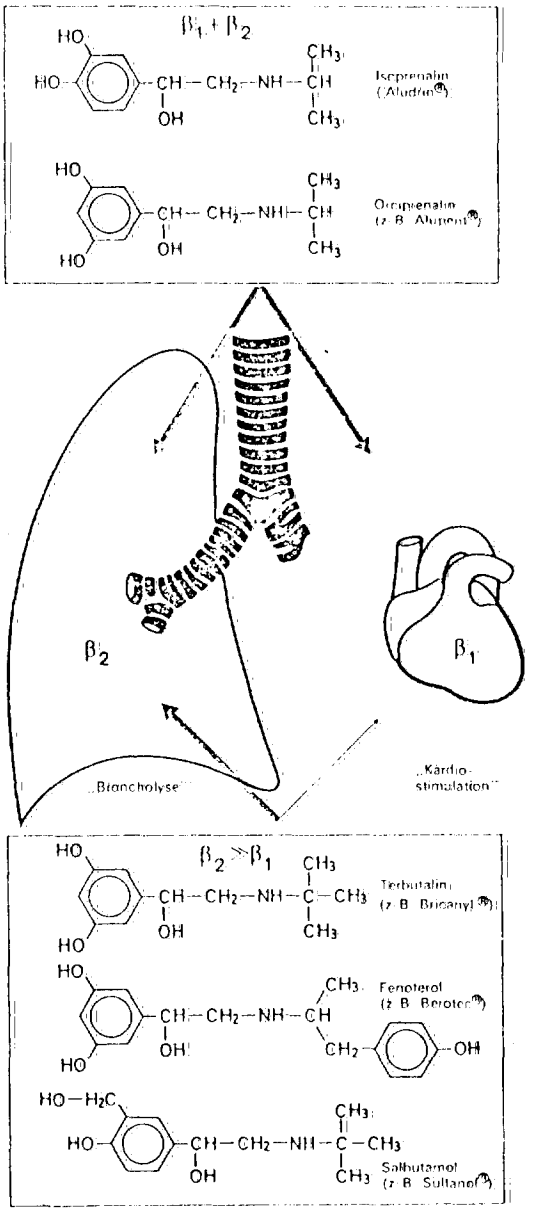

Abb. 12: Wirkungen von β-Sympathomimetika auf Herz und Bronchialtrakt.
β-Sympathomimetika führen über eine Erregung der kardialen β_1-Rezeptoren zu einer positiv chronotropen, inotropen und dromotropen Wirkung („Kardiostimulation"), und über eine Erregung der β_2-Rezeptoren an der glatten Muskulatur der Bronchiolen zur „Bronchospasmolyse"; auch die Dilatation der Arteriolen (Senkung des peripheren Gefäßwiderstandes) und die Erschlaffung der Uterusmuskulatur („Tokolyse") sind β_2-sympathomimetische Wirkungen. Einige β-Sympathomimetika (Terbutalin, Fenoterol, Salbutamol) erregen β_2-Rezeptoren stärker als β_1-Rezeptoren.

(Forth, W., Henschler, D., Rummel, W. (Eds.), Allgem. und spez. Pharmakologie und Toxikologie, 2. Auflage, Mannheim/Wien/Zürich: Bibliographisches Institut, 1979)+

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